IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ARBUTUS BIOPHARMA CORP. and GENEVANT SCIENCES GMBH, Plaintiffs, v. PFIZER INC. and BIONTECH SE, Defendants.	Civil Action No. 3:23-1876-ZNQ-TJB *Document Filed Electronically* Jury Trial Demanded

PLAINTIFFS' OPENING MARKMAN BRIEF

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I. INTRODUCTION

The inventions of the asserted patents address the most challenging problem that had vexed the nucleic acid drug development field for decades: how to deliver nucleic acid (such as DNA or mRNA) therapeutics to cells, where they can exert their desired effect, without being degraded by enzymes in the bloodstream. Two patent families focusing on the solution to this problem are at issue in this case.

One of the patent families ("Lipomixer Patents") includes three asserted patents. U.S. Patent No. 9,504,651 (the "'651 patent") claims novel lipid vesicles with certain lipid components and mRNA. Two other patents in this family, U.S. Patent Nos. 11,298,320 (the "'320 patent") and 11,318,098 (the "'098 patent"), share the same specification as the '651 patent and claim novel apparatuses and methods to synthesize those lipid vesicles. These innovative techniques yield lipid vesicles with beneficial properties and facilitate better protection of the nucleic acids contained inside the vesicles, thereby protecting the nucleic acid from degradation when the lipid vesicles are administered to people.

The other patent family ("Lipid Composition Patents") includes U.S. Patent Nos. 8,492,359 (the "'359 patent") and 11,141,378 (the "'378 patent"), which share the same specification and claim novel nucleic acid-lipid nanoparticles ("LNPs"). These LNPs are specifically designed to protect and deliver nucleic acid contained inside the LNP, such as the mRNA in Defendants' vaccine, to their intended cellular targets. Without the protection of an LNP, the mRNA would degrade rapidly in the body and be ineffective. The LNPs include specified lipid components: a "cationic" lipid, which exhibits a positive charge under certain conditions; one or two "non-cationic" lipids, such as a phospholipid or cholesterol; and a "conjugated" lipid, such as a polyethyleneglycol (PEG)-lipid, that inhibits aggregation of particles. *E.g.*, '378 patent, 48:30-

59:23; Thompson Decl. ¶ 21. The ratio of the lipid components—typically expressed on a mole[1] percent (mol %) basis of the total lipid in the particle—can affect the properties of the LNPs. The Lipid Composition Patents disclose and claim novel lipid combinations and ratios that result in nucleic acid-LNP compositions with improved efficacy and tolerability.

II. ARGUMENT

A. "lipid vesicle" / "vesicle" ('651 patent, '320 patent, '098 patent)

Plaintiffs' proposed construction	Defendants' proposed construction
"lipid vesicle" means "a lipid composition that can be used to deliver a compound" Alternatively, "vesicle" means "a composition that can be used to deliver a compound"	"vesicle" means "a sac containing an aqueous interior or a relatively disordered lipid mixture"
'651 Patent, Claims 1-14; '320 Patent, Claims 1, 3, 6, 7, 12, 16, 17, 18, 21, 22, 26, 30; '098 Patent, Claims 1, 3, 6, 7, 12, 16, 17, 18, 21, 22, 26, 30	

As an initial matter, the parties dispute whether the Court should construe the term "lipid vesicle" (as Plaintiffs contend) or the term "vesicle" (as Defendants contend). The term is used in the context of claim 1 of the '651 patent as follows:

> 1. A ***lipid vesicle*** formulation comprising:
>
> (a) a plurality of ***lipid vesicles***, wherein each ***lipid vesicle*** comprises:
> a cationic lipid;
> an amphipathic lipid; and
> a polyethyleneglycol (PEG)-lipid; and
> (b) messenger RNA (mRNA), wherein at least 70% of the mRNA in the formulation is fully encapsulated in the ***lipid vesicles***.

'651 patent claim 1 (emphases added). Plaintiffs assert that "lipid vesicle" is the proper term for construction for two reasons. First, the patent claims all recite "lipid vesicle"—*i.e.*, a vesicle made from lipids—not just any "vesicle," *see* '651 patent claims 1-14; '320 patent claims 1, 3, 6, 7, 12,

[1] A mole ("mol") is a standard unit of measurement that refers to the number of molecules present.

16, 17, 18, 21, 22, 26, 30; '098 patent claims 1, 3, 6, 7, 12, 16, 17, 18, 21, 22, 26, 30. Second, the patent explicitly defines the term "lipid vesicle," and Plaintiffs' proposed construction reflects this express definition.

In contrast, Defendants strip the word "vesicle" of all context and propose a construction of that term based on a non-technical dictionary definition. Defendants attempt to pay lip service to the specification by including some, but not all, of the non-limiting examples of **"**lipid vesicles" set forth in the patent, but all of these examples follow the express definition of "lipid vesicle" put forth by Plaintiffs.

The Court should adopt Plaintiffs' proposed construction because the patentee's own definition governs and because the intrinsic evidence fails to support Defendants' efforts to ignore that definition.

1. The court should construe the term "lipid vesicle" in accordance with the specification's express definition

"When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009). The '651 patent specification contains a section titled "Definitions." '651 patent at 3:48-5:44. Within that section is an express definition for "lipid vesicle":

> ***"Lipid vesicle" refers to any lipid composition that can be used to deliver a compound*** including, but not limited to, liposomes, wherein an aqueous volume is encapsulated by an amphipathic lipid bilayer; or wherein the lipids coat an interior comprising a large molecular component, such as a plasmid, with a reduced aqueous interior; or lipid aggregates or micelles, wherein the encapsulated component is contained within a relatively disordered lipid mixture.

Id. at 5:30-37 (emphasis added). Thus, the specification defines "lipid vesicle" as "***any*** lipid composition that can be used to deliver a compound," and then goes on to provide non-limiting examples of lipid vesicles and their characteristics.

These disclosures indicate the patentee's clear intention as to the meaning of "lipid vesicle." Not only is the above passage in the definition section of the patent, but courts have also consistently determined that the phrase "refers to" in the intrinsic record indicates an intention to define the term. For example, the Federal Circuit explained in *Parkervision, Inc. v. Vidal* that "[t]he patentee's use of the phrases 'as used herein' and 'refer to' conveys an intent for [claim term] to be definitional." 88 F.4th 969, 976 (Fed. Cir. 2023). Similarly, the court explained in *Vasudevan Software, Inc. v. MicroStrategy, Inc.* that "[a]n applicant's use of the phrase 'refers to' generally indicates an intention to define a term." 782 F.3d 671, 679 (Fed. Cir. 2015).

The Court should construe the term "lipid vesicle" in accordance with the specification's definition to mean "a lipid composition that can be used to deliver a compound."[2]

2. Defendants' proposed construction of "vesicle" is inconsistent with the patent specification

Defendants' proposed construction should be rejected. First, Defendants rely on extrinsic evidence to change the meaning of "vesicle" from "any composition" to a "sac." Specifically, Defendants import that word "sac" based on a non-technical dictionary definition from The New Oxford American Dictionary. Ex. 6. But the express definition in the specification for "lipid vesicle," and thus "vesicle," refers to "any composition." It is not limited to a "sac."

Second, Defendants' construction introduces a new, undefined word that is found nowhere in the intrinsic evidence. The word "sac" comes from a non-technical dictionary unrelated to the subject matter at issue and would create ambiguity, not clarity. Indeed, the same dictionary defines

[2] If the Court decides to construe "vesicle," the Court should construe it to mean "a composition that can be used to deliver a compound." The term "vesicle" is used only in the context of "lipid vesicles." Thus, the only meaning of "vesicle" consistent with the specification would be "a composition that can be used to deliver a compound." The preceding term "lipid" in the claims would then limit the term in the precise manner of the specification's definition.

the word "sac" to mean "a hollow, flexible structure resembling a bag or pouch," which has no applicability here. Ex. 7. Defendants' proposed construction would simply create confusion for the jury and should be rejected on that basis. *See Carefusion 303, Inc. v. Hospira, Inc.*, No. 11-CV-762-RGA, 2013 WL 508917, at *3 (D. Del. Feb. 11, 2013) ("Carefusion's proposed construction, however, is confusing because it introduces two undefined terms").

Third, Defendants' proposed construction requires either "an aqueous interior" or "a relatively disordered lipid mixture." But these characteristics appear as examples clearly identified as non-limiting in the definition of "lipid vesicle," which Defendants seek to ignore:

> ***"Lipid vesicle"*** refers to any lipid composition that can be used to deliver a compound including, ***but not limited to***, liposomes, wherein ***an aqueous volume*** is encapsulated by an amphipathic lipid bilayer; or wherein the lipids coat an interior comprising a large molecular component, such as a plasmid, with a reduced aqueous interior; or lipid aggregates or micelles, wherein the encapsulated component is contained within a ***relatively disordered lipid mixture***.

Id. at 5:30-37 (emphases added). Defendants' construction should thus be rejected, as "a claim construction must not import limitations from the specification into the claims." *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1354 (Fed. Cir. 2012).

B. The "fully encapsulated" terms

The parties dispute the meaning of "fully encapsulated" in two different patent families, the Lipomixer patents (the '651 patent specifically) and the Lipid Composition patents (the '359 patent and '378 patent specifically). The two patent families have different specifications, but consistently use the term "fully encapsulated" to refer to mRNA contained inside lipid vesicles or lipid particles. Plaintiffs propose construing the term separately in each patent family, however, because of the differing context of the claims of the respective patents in which the term appears. The claims in the '651 patent refer to the percentage of mRNA ***in the formulation*** that is fully encapsulated, whereas the claims in the '359 patent and '378 patent refer to a nucleic acid-lipid

particle that contains an mRNA that is fully encapsulated. In both instances, however, the key concept is that the mRNA is "contained inside" the lipid vesicles or lipid particle, as set forth in Plaintiffs' proposed constructions and supported by the intrinsic evidence.

1. "wherein at least 70% / at least 80% / about 90% of the mRNA in the formulation is fully encapsulated in the lipid vesicles" ('651 patent")

Plaintiffs' Proposed Construction	**Defendants' Proposed Construction**
"wherein at least 70% / at least 80% / about 90% of the mRNA is in the formulation is contained inside the lipid vesicles." Alternatively, "fully encapsulated" means "contained inside."	Indefinite.[3]
'651 Patent, Claims 1, 13, 14	

A person of ordinary skill in the art ("POSA") would have understood that the full claim term at issue delineates (1) the ***location*** of the mRNA (*i.e.*, fully encapsulated), and (2) the ***proportion*** of mRNA fully encapsulated in the lipid vesicles (*i.e.*, at least 70% / 80% or about 90%). Thompson Decl. ¶ 43.

With respect to the first issue, a POSA would have recognized that "fully encapsulated" refers to the mRNA being ***contained inside*** the vesicle. *See* Thompson Decl. ¶ 44. Consistent with the understanding in the field, the specification describes lipid systems where the nucleic acid is in different locations. In some, such as liposome complexes (*i.e.*, "lipoplexes") or lipid aggregates, the nucleic acid is part of "a relatively disordered lipid mixture"—akin to, for example, spaghetti (nucleic acid) interspersed with meatballs (lipids). '651 Patent at 5:35-37; *see* Thompson Decl. ¶¶ 20, 45; Ex. 8 (Sternberg 1994) at 364 (Figure 2). Alternatively, the nucleic acid can be on the

[3] On May 6, 2024, the Court ordered that indefiniteness will not be addressed as part of *Markman* and that the parties need not brief the issue at this stage. D.I. 70. Defendants have not proposed any updated construction to date.

"interior"—that is, contained ***inside***—the vesicles. '651 Patent, 5:30-35, 5:41-45; Thompson Decl. ¶¶ 45-47; Ex. 9 (MacLachlan 2007) at 242 ("[I]t is important to distinguish first-generation 'lipoplex' or 'oligoplex' systems from those that truly encapsulate their NA payload."). The specification further characterizes these distinct lipid systems, where the nucleic acid is in different locations, as representing "partial encapsulation" or "full encapsulation." '651 Patent at 5:38-40. The claims are directed to the latter: systems where mRNA is in the interior, contained inside the vesicle, and not merely part of "a relatively disordered lipid mixture." *Compare* '651 Patent at 5:30-35 *with* 5:35-37; *see* Thompson Decl. ¶¶ 46-47, 51; Ex. 9 (MacLachlan 2007) at 239; Ex. 14 (5/12/2015 Response) at 6-8.

The prosecution history also establishes that "fully encapsulated" refers to the location of the nucleic acid inside the claimed lipid vesicles. Thompson Decl. ¶¶ 48-51. The examiner initially rejected the claims, including the "fully encapsulated" language, over the Unger reference. Ex. 13 (2/13/2015 Non-Final Rejection) at 5. The applicant explained that Unger used lipoplexes, "in which little, if any, of the DNA payload is encapsulated ***within*** the preformed cationic liposomes," and instead "is merely ***associated with the surface*** of the preformed liposome." Ex. 11 (10/22/2014 Response) at 6-7 (emphases added). Unger thereby differed from "the encapsulated mRNA present ***within the lipid vesicles*** of the present invention" that would be "protected from nuclease degradation upon systemic administration." *Id.* And the applicant concurrently submitted a declaration that drew the same distinction. Ex. 11 (10/22/2014 Decl.) ¶ 10.

With respect to the second issue, a POSA would have recognized that the limitation as a whole refers to the ***proportion*** (i.e., at least 70% / 80% or about 90%) of mRNA that is contained inside the lipid vesicles, a measurement commonly known as "encapsulation efficiency." Thompson Decl. ¶ 52, 56-59. For instance, the specification repeatedly reports the favorable

encapsulation efficiencies the inventors achieved, including the very encapsulation percentages recited in the claims. *See, e.g.*, '651 Patent at 2:51-54 ("encapsulation efficiency is as high as about 90%"), 8:7-11 (the disclosure "herein provides for encapsulation of therapeutic agent in the formed liposome . . . with an encapsulation efficiency of up to about 90%"), 9:24-26, 36-38 (disclosing 70-80% of "therapeutic agent entrapment"), 12:64-13:1 ("the processes and apparatus of the present invention provide an encapsulation efficiency . . . of up to about 90%"), 15:32-33, 18:40-42, Figures 5-8 (showing measured encapsulation efficiencies of at least 70%, at least 80%, and up to about 90%).

During prosecution, the applicant and examiner discussed methods of measuring encapsulation efficiency that further confirm "fully encapsulated" refers to the location of the mRNA ***inside*** the claimed lipid vesicles. The examiner rejected the claims over WO 98/51278 (published Nov. 19, 1998) ("Semple"), finding that Semple disclosed nucleic acids "enclosed by the lipid vesicle (i.e., protected from degradation)." Ex. 13 (2/13/15 Rejection) at 7. Specifically, Semple described measuring encapsulation efficiency using a "fluorescent dye binding assay" and reported encapsulation efficiencies of greater than 50%. Ex. 23 (Semple) at 36:1-4, 13:24-29; Thompson Decl. ¶ 60. As Dr. Thompson explains in his declaration, the use of a fluorescent dye that binds to nucleic acid is a standard method of measuring encapsulation efficiency. Thompson Decl. ¶ 55. In brief, the dye first is added to the mixture of lipid vesicles and fluorescence is measured. Thompson Decl. ¶ 69. Because the dye is lipid impermeable—it cannot pass through lipids and thus cannot access, interact with, or detect nucleic acid ***contained inside*** the lipids—the fluorescence is a measurement of the amount of nucleic acid outside the lipids. *Id.* Subsequently, a POSA adds a detergent to degrade the lipid barrier, which releases the nucleic acid (which the dye, before detergent was added, could not reach). *Id.* A POSA then measures

fluorescence again, to ascertain the total amount of nucleic acid (that was previously both inside and outside the lipid vesicles). *Id.* From those values, a POSA can calculate the proportion of nucleic acid that was contained inside the lipid vesicle. *Id.* The applicant ultimately overcame Semple by amending the claims to require encapsulation efficiencies higher than those disclosed in Semple. Ex. 16 (8/18/2015 Response) at 8 ("Importantly, the **very low encapsulation efficiency** associated with the method of Semple *et al.* is **well below** the minimum mRNA encapsulation efficiency required in the presently claimed formulations.") (emphasis in original), Thompson Decl. ¶ 64.

Accordingly, the applicant and examiner both understood that the claimed percentages of mRNA "fully encapsulated in the lipid vesicles" could be measured using the standard dye assay, demonstrating that they also shared an understanding of what it means for mRNA to be fully encapsulated: the nucleic acid is contained inside the lipid vesicles such that it could not be reached by outside molecules such as the fluorescent dye. Thompson Decl. ¶¶ 60-68. Indeed, in distinguishing the lipoplexes of Unger, the applicant similarly explained that mRNA encapsulated within the lipid vesicles as claimed would be "protected" from degrading enzymes in the body. Ex. 11 (10/22/14 Response) at 7 ("Dr. Heyes explains that the encapsulated mRNA present within the lipid vesicles of the present invention will be protected from nuclease degradation upon systemic administration, while nucleic acid that is merely associated with the surface of a preformed liposome (such as the DNA of the lipoplexes of Unger et al.) will be more readily degraded by serum nucleases"); Ex. 11 (10/22/14 Decl.) ¶ 10.

This term was recently construed in co-pending litigation ("Moderna litigation") by another district court in this Circuit in *Arbutus Biopharma Corp. et al. v. Moderna, Inc. et al*, No. 1:22-CV-00252-MSG, 2024 WL 1434526 (D. Del. Apr. 3, 2024) ("*Arbutus Delaware*"). There, the

Court combined the parties' proposed constructions and defined the term to mean "wherein at least 70%/at least 80% about 90% of the mRNA in the formulation is fully, as distinct from partially, contained inside the lipid vesicles." *Id.* at *18. Plaintiffs agree that fully encapsulated means "contained inside," consistent with the Court's construction in the Moderna litigation. However, Plaintiffs respectfully disagree with the portion of the Court's construction that refers to the percentage of "mRNA in the formulation that is fully, as distinct from partially" contained inside the vesicles to the extent it is interpreted to mean that the percentage of fully encapsulated mRNA should be determined on a complete individual mRNA molecule-by-complete individual mRNA molecule basis and to refer to the proportion of individual mRNA molecules that are completely inside lipid vesicles rather than the fraction of total mRNA ***in the formulation*** that is contained inside the lipid vesicles. Nothing in the intrinsic record suggests that this is what was meant by "partial encapsulation," *see* '651 patent at 5:38-40, nor do Defendants here propose the "fully, as distinct from partially" construction here as the defendants in the Moderna litigation did. *Arbutus Delaware*, 2024 WL 1434526, at *16. Instead, as discussed above and consistent with the file history, in the one instance that term is used in the '651 patent, "partial encapsulation" refers to nucleic acid molecules that are located within a "relatively disordered lipid mixture," but not actually contained inside the vesicles at all. Thompson Decl. ¶ 46.

Indeed, the Defendants in this case do not propose "fully, as distinct from partially"—or any other alternate construction for these "fully encapsulated" terms—at all. This constitutes another reason the Court's construction from the Moderna litigation should not be adopted verbatim here. Defendants' gamesmanship to seek no construction where the specification and prosecution history give the terms clear meaning is contrary to the purpose of claim construction—that is, to "determine the meaning and scope of the patent claims," *O2 Micro Intern. Ltd. v. Beyond*

Innovation Tech. Co., 521 F.3d 1351, 1360 (Fed. Cir. 2008)—and violates the canon that "courts should attempt to construe claims to preserve their validity." *Omega Engineering, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1335-36 & n.6 (Fed. Cir. 2003) (reversing construction that would render claims indefinite).

Plaintiffs' proposed construction clarifies the meaning and scope of this claim term. Defendants have not even proposed a construction. The Court should adopt Plaintiff's construction.

2. "fully encapsulated" ('359 patent and '378 patent)

Plaintiffs' Proposed Construction	**Defendants' Proposed Construction**
"contained inside"	"the active agent or therapeutic agent in the lipid particle is not significantly degraded after exposure to serum or a nuclease or protease assay that would significantly degrade free DNA, RNA, or protein, which is indefinite"
'359 Patent, Claim 20; '378 Patent, Claims 9, 11, 20, 22, 27	

A POSA would understand that "fully encapsulated" in the '359 patent and '378 patent also refers to mRNA contained inside the vesicle. *See* Thompson Decl. ¶¶ 70–74. The shared specification of the '359 patent and '378 patent confirms that the inventors intended to use the term "fully encapsulated" to describe a nucleic acid contained inside the claimed lipid particle. The specification consistently describes full encapsulation "in" or "within" the lipid. '359 Patent at 11:30-31 ("is fully encapsulated ***within*** the lipid"); 11:62-65 ("the nucleic acid is fully encapsulated ***in*** the lipid particle"); 27:47-49 (same); Thompson Decl. ¶ 72.

The '359 patent and '378 patent also expressly disclose that "full encapsulation may be determined by an Oligreen® assay. Oligreen® is an ultra-sensitive fluorescent nucleic acid stain for quantitating oligonucleotides and single-stranded DNA or RNA in solution . . ." '359 Patent at 23:16-20. A POSA would understand that the results of these assays quantify how much mRNA

is contained inside the vesicles, consistent with the discussion of encapsulation efficiencies during prosecution of the '651 patent. *See* Thompson Decl. ¶ 73.

Thus, consistent with the usage of the term "fully encapsulated" in the '651 patent and file history,[4] "fully encapsulated" in the claims of the '359 and '378 patents should also be defined to mean "contained inside." *See Nanoco Techs. Ltd. v. Samsung Elecs. Co., Ltd.*, No. 2:20-CV-00038-JRG, 2021 WL 1890453, at *5 (E.D. Tex. May 11, 2021) (adopting "a single construction for all relevant patents" and finding "there is no compelling reason to have different constructions between the different patents, as they have substantially similar specifications and the disputed term is used in the same way in the claims across the patents"); *see also SightSound Technologies, LLC v. Apple Inc.*, 809 F.3d 1307, 1317-18 (Fed. Cir. 2015) (giving same construction to common terms in two related child patents); *In re Varma*, 816 F.3d 1352, 1363-64 (Fed. Cir. 2016) ("[T]he principle that the same phrase in different claims of the same patent should have the same meaning is a strong one, overcome only if 'it is clear' that the same phrase has different meanings in different claims.").

Defendants' proposed construction should be rejected because it simply parrots language from the specification describing the benefits of fully encapsulated mRNA, without clarifying what the claim term means. Defendants do not propose their construction to aid the jury in understanding the claim scope, which is the goal of claim construction. "The purpose of claim construction is to reduce ambiguity for the jury." *Vivus, Inc. v. Actavis Lab'ys FL Inc.*, No. 14-CV-3786-SRC-CLW, 2016 WL 3919455, at *3 (D.N.J. July 20, 2016). In fact, Defendants intend to argue ***their own***

[4] The specification of the '378 patent and '359 patent includes the same single reference to "partial encapsulation" as the '651 patent. Like the passage in the '651 patent, a POSA would understand that "partial encapsulation" refers to a scenario where mRNA is located within a relatively disordered lipid mixture, but not contained inside the vesicles themselves. *See, e.g.*, '359 patent at 11:59-62.

construction is indefinite, with which Plaintiffs disagree. The specification does disclose that "[t]he term 'fully encapsulated' ***indicates*** that the active agent or therapeutic agent in the lipid particle is not significantly degraded after exposure to serum or a nuclease or protease assay that would significantly degrade free DNA, RNA, or protein." '359 patent at 23:6-10 (emphasis added). But this does not define the term "fully encapsulated" any more than saying that someone is tall "indicates she can reach higher shelves at the grocery store" defines what it means to be tall.

The specification further states that "'fully encapsulated' ***also indicates that the lipid particles are serum-stable***, that is, that they do not rapidly decompose into their component parts upon in vivo administration." '359 Patent at 23:21-24 (emphasis added). While Defendants attempt to import this also into the definition of "fully encapsulated," serum-stability is just another potential benefit of full encapsulation of mRNA, rather than a definition. *I4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 843-44 (Fed. Cir. 2010) (rejecting defendant's proposed construction because the specification's statements were "best understood as describing the advantages of separate storage" and "not every benefit flowing from an invention is a claim limitation"); *Seismic Structural Design Assocs., Inc. v. Gensler*, No. 11-CV-004472-SJO-SSX, 2013 WL 12122303, at *7 (C.D. Cal. Jan. 17, 2013) ("The fact that the slots in Plaintiff's Claims might serve a particular function does not mean that this function becomes part of the definition of the word 'slot.' The benefits of the invention need not be recited in every claim.").

Accordingly, the Court should reject Defendants' proposed construction and construe "fully encapsulated" to mean "contained inside."

C. Mol % terms ('359 patent)

Plaintiffs' proposed construction	Defendants' proposed construction
"a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle" has its plain and ordinary meaning, *i.e.*, "a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle" "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle" has its plain and ordinary meaning, *i.e.*, "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle" The recited mol % ranges in the above terms are understood to encompass their standard variation based on the number of significant figures recited in the claim	"a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle" means "an amount of cationic lipid that is no less than 50% and no more than 65% of the total lipid present in the particle" "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle" means "an amount of cholesterol or derivative thereof that is no less than 30% and no more than 40% of the total lipid present in the particle"
'359 Patent, Claim 1	

For the terms "a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle" and "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle," the parties do not dispute the meaning of the words, but rather the precision of the claimed mol % ranges. Plaintiffs' proposed construction adheres to the standard scientific convention of significant figures and rounding that is applied consistently by the courts, meaning that 49.5% would round up to a stated value of "50%". Defendants disagree with Plaintiffs' position, which allows for rounding, and propose a construction that requires an amount that is "no less than" the lower end of the range and "no more than" the upper end of the range. Defendants' construction would effectively insert a decimal after the recited value and add multiple zeroes such that "50%" would become "50.000%," or an even more precise number,

thereby improperly limiting the literal scope of the claimed numerical percentage. Defendants' construction, for example, would not result in 49.999% rounding up to "50%".

Claim 1 of the '359 patent recites these two disputed terms and is reproduced below:

> 1. A nucleic acid-lipid particle comprising:
>
> (a) a nucleic acid;
> (b) ***a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle***;
> (c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 3 mol % to 15 mol % of the total lipid present in the particle and the ***cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle***; and
> (d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle.

'359 patent claim 1 (emphases added).

Another district court in this Circuit has already ruled in favor of Plaintiffs on this precise issue for the same '359 patent-in-suit. In *Arbutus Delaware*, the court construed claim terms from several patents, including the '359 patent at issue here. 2024 WL 1434526 at *2. Among the terms construed by the *Arbutus Delaware* court was "___ mol % of the total lipid present in the particle."[5] *Id.* at *4. The parties in that case disputed whether numerical terms included rounding, such that, for example, the claim term "50%" includes a measurement of 49.8%, which rounds up to "50%" based on two significant digits in the numerical claim term.

Plaintiffs argued the same position there as here, that "the plain meaning of the numbers in its claims adheres to the standard scientific conventions of significant figures and rounding." *Id.* at *8. Defendant Moderna opposed, arguing—as Defendants Pfizer and BioNTech do here—that

[5] The same claim term appears in U.S. Patent Nos. 8,058,069 (the "'069 patent"), 8,822,668, and 9,364,435, which were at issue in the *Arbutus Delaware* case but are not at issue here, as well as in the '378 patent. These patents are all in the same family as the '359 patent and share the same specification.

the recited mol % ranges are understood as the exact ranges recited in the claim, meaning that the patent allows for no deviation above the high end or below the low end of the range. *Id.* The *Arbutus Delaware* court carefully analyzed the specification, relevant file history, expert testimony, and applicable case law, and adopted Plaintiffs' construction that "the recited 'mol %' ranges are understood to encompass their standard variation based on the number of significant figures recited in the claim." *Id.* at *13.

Plaintiffs submit that consistent with Federal Circuit precedent, this Court should likewise adopt a construction for the numerical claim terms that encompasses standard variation based on the number of significant figures recited in the claim.

1. The standard scientific meaning of a numerical term encompasses significant figures and rounding

The Federal Circuit has repeatedly held that the literal scope of numbers in claims adheres to the standard scientific convention of significant figures and rounding. *See, e.g., U.S. Philips Corp. v. Iwasaki Elec. Co.*, 505 F.3d 1371, 1377-78 (Fed. Cir. 2007); *Par Pharm., Inc. v. Eagle Pharms., Inc.*, 44 F.4th 1379, 1382 (Fed. Cir. 2022).

Significant figures are the digits in a number that indicate its precision, such that when compared to other numbers expressed with additional digits, those other numbers are rounded to the last significant figure. Thompson Decl. ¶¶ 23-25. For example, the number 0.91 includes two significant digits after the decimal point. Thus, when stated as two significant digits after the decimal point, a measurement of 0.905 would round up to 0.91, whereas a measurement of 0.904 would round down to 0.90 when stated as two significant digits. Likewise, a measurement of 0.914 would round down to 0.91, whereas a measurement of 0.915 would round up to 0.92. Accordingly, the term "0.91" in a claim would literally encompass "between 0.905 and 0.914, based on the

reasoning that numbers in this range would be rounded to 0.91." *Viskase Corp. v. Am. Nat. Can Co.*, 261 F.3d 1316, 1320 (Fed. Cir. 2001).

If a patentee desires to limit its claims to greater precision, it can do so by including more significant digits. For example, the term "'1.0' may be said to have more significant digits than '1' with no decimal point." *Iwasaki*, 505 F.3d at 1377. A measurement of 1.16 stated as one significant digit after the decimal point would round up to 1.2. In contrast, the same measurement of 1.16 stated with no significant digits after the decimal point would round down to "1". Accordingly, based on scientific notation and rounding, "[i]t is technically incorrect to assert" a "greater precision" than what is "reflected in the recitation of a significant digit following the decimal point." *Id.* at 1377-78.

The rules of rounding apply as well to a range of numbers, specifically to the value at the end of the range. In *Par Pharm.*, 44 F.4th at 1382, the Federal Circuit affirmed a ruling where a claim reciting a pH range of 3.7-3.9 was construed to encompass a range of 3.65-3.94. In *Actelion Pharms. LTD v. Mylan Pharms. Inc.*, 85 F.4th 1167 (Fed. Cir. 2023), the question before the Court was the meaning of "a pH of 13 or higher." *Id.* at 1170. The district court construed the claim term as including a range of 12.5 or higher based on the rules of significant figures, while the defendant argued that the claim term created an absolute floor at 13 beneath which the pH could not fall. *Id.* The Federal Circuit rejected defendant's argument that the claim language was not subject to the rules of rounding because it involved a range, holding that "there is no blanket rule that ranges, or specifically open-ended ranges, must foreclose rounding." *Id.* at 1171.

Following Federal Circuit precedent, district courts, including in this Circuit, regularly apply rounding in patent claims. *E.g.*, *Noven Pharms., Inc. v. Actavis Labs. UT, Inc.*, No. 15-CV-249-LPS, 2016 WL 3625541, at *3 (D. Del. July 5, 2016) ("15 mg/cm^2" means "15 plus or minus

at least .5"); *Par Pharm., Inc. v. Eagle Pharms. Inc.*, No. 18-CV-0823-CFC-JLH, 2021 WL 3886418, at *3 (D. Del. Aug. 31, 2021); *Johnson Matthey Inc. v. Noven Pharms., Inc.*, No. 2:07-CV-260-CE, 2009 WL 2208214, at *7, *9 (E.D. Tex. July 21, 2009) (construing "41-42° C" to have its "literal range" of "between 40.5° C and 42.4° C").

This "standard scientific convention" straightforwardly applies to the literal scope of Plaintiffs' claims at issue here. Applying this convention to the claim terms at issue based on the number of significant figures recited, a POSA would understand that "a cationic lipid comprising from 50 mol % to 65 mol %" encompasses 49.5-65.4$\overline{9}$ mol % cationic lipid and that "the cholesterol or derivative thereof comprises from 30 mol % to 40 mol %" encompasses 29.5-40.4$\overline{9}$ mol % cholesterol. Thompson Decl. ¶ 80. A POSA would understand that these are the encompassed ranges based on the number of significant figures recited in the claim terms. *Id.*

In contrast, if the claim recited "50.0 mol %," 49.5% would not round up, but 49.95% would round up (to 50.0%). Thompson Decl. ¶ 80 n.22. Yet, Defendants' construction does not allow for rounding, so that even 49.999 mol % would not fall within the claimed range, violating Federal Circuit precedent by "stat[ing] the endpoints of the claimed range with greater precision than the claim language warrants." *Iwasaki*, 505 F.3d at 1377. Courts routinely reject efforts like Defendants' to limit numbers and ranges to their "exact" or "precise" limits devoid of any rounding. *See, e.g., id*; *Noven*, 2016 WL 3625541, at *3 (construing claim not to require "precisely 15.0 mg/cm2"); *Unimed Pharms. LLC v. Perrigo Co.*, No. 13-CV-236-RGA, 2015 WL 1094601, at *6-7 (D. Del. Mar. 11, 2015) ("'exactly' is unnecessary and needlessly adds a limitation" to "1.0% to 10.0% (w/w) of 0.1 N sodium hydroxide"); *Otsuka Pharm. Co. v. Lupin Ltd.*, No. 21-CV-900-RGA, 2022 WL 2952759, at *2 (D. Del. July 26, 2022) ("I reject any construction intended to connote greater precision than '1 mole per 1 mole' or '0.25 [moles] . . . per 1 mole.'").

Nothing in the intrinsic record reflects an intent to deviate from standard scientific convention and limit "50 mol %" to a more precise figure, such as "50.000%."

2. The specification shows an intent to apply the rules of significant figures

The specification is clear, controlling, and reflects an intent to apply the rules of significant figures. It uses additional significant figures, including trailing zeros, to convey additional precision where desired, consistent with rules of rounding. For example, Table 2 of the specification specifies ratios using different numbers of significant figures for the lipid components. *E.g.*, '359 patent at 69:41-64. Sample No. 1 is "2"% PEG (conjugated lipid), "40"% DLinDMA (cationic lipid), "10"% DPPC (phospholipid), and "48"% cholesterol. *Id.* Sample 10, by contrast, uses "1.**3**"% conjugated lipid, 53.**3**"% cationic lipid, 13.**3**"% phospholipid, and "32.**0**"% cholesterol. *Id.* (emphases added).

The trailing zero after the decimal point in "32.0"% cholesterol is especially crucial—it confirms that the inventors used significant figures as intended: 32.0% conveys a different degree of precision and rounding than 32%. Table 2 reflects this usage repeatedly across every lipid component: Sample No. 3 ("27.**0**"% cationic lipid), Sample No. 7 ("64.**0**" cholesterol), Sample No. 8 ("25.**0**"% cationic lipid and "60.**0**"% cholesterol), Sample No. 12 ("1.**0**"% conjugated lipid), Sample No. 13 ("7.**0**"% phospholipid). *Id.* (emphases added). And Table 4 reflects the same use of significant figures and trailing zeros in Group No. 8 ("27.**0**"% cationic lipid), and Group No. 10 ("25.**0**"% cationic lipid and "60.**0**"% cholesterol"), while Group Nos. 2, 4, 5, and 13 recite integers with no post-decimal point zeros. *Id.* at 71:33-67 (emphases added).

As recognized in the *Arbutus Delaware* decision, "the specification substantiates Plaintiffs' construction." 2024 WL 1434526 at *10. The court explained that "the inventors demonstrated that they knew how to use additional significant numbers past a decimal point" and cited the

numbers in Table 2 that included trailing zeroes. *Id.* "Had the inventors intended to not rely on the rules of rounding and significant figures, they would not need to have written the whole numbers in Table 2 with any trailing zeroes." *Id.*

There is simply no reason to use numbers like "40" in one instance and "60.0" in another, other than to convey that the latter has more significant digits for rounding purposes than the former. Otherwise, the inventors would have reported the values in the same way, such as 40 and 60. Thompson Decl. ¶ 79. The specification's use of additional significant figures, including trailing zeros, to convey additional precision where desired—consistent with the rules of rounding—is controlling. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005), ("construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction") (citation omitted). The recitation of whole numbers, such as "50", in the claims without a decimal point and without a trailing zero signals a clear intention to require less precision than "50.0". Yet, Defendants' proposed construction would in effect add the precision of multiple trailing zeros where there are none.

The specification does not in any manner support adding the precision that Defendants propose. Courts have done so where the specification or file history showed that the patentee "relie[d] on [additional] significant figure[s] . . . to distinguish [the invention] from the prior art," *Viskase*, 261 F.3d at 1321-22, "treated [a less precise number] as if it were [more precise]," *id.* ("0.91" g/cm3 as "0.910" g/cm3), "repeatedly differentiate[d] between formulations" that would be the same without adding additional significant figures, *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1334 (Fed. Cir. 2021) (the patent contrasted "0.001% w/w PVP" with "0.0005% w/w PVP"), or where rounding would make it "impossible" to reconcile with the specification,

Takeda Pharm. Co. v. Zydus Pharm. USA, Inc., 743 F.3d 1359, 1364 (Fed. Cir. 2014). None of those fact patterns applies here. Thompson Decl. ¶ 85.

3. The file history does not support Defendants' proposed construction

Nothing in the file history shows that Plaintiffs used the claimed mol % terms with more precision than the recited number of significant figures, let alone the "clear and unmistakable disavowal of scope" required to displace the ordinary meaning. *Grober v. Mako Products, Inc.*, 686 F.3d 1335, 1341 (Fed. Cir. 2012); *see also Viskase*, 261 F.3d at 1321-22. During prosecution the '069 patent[6] application, the patentee submitted claims reciting "a cationic lipid comprising from ***about*** 50 mol % to ***about*** 65 mol % of the total lipid present in the particle." Ex. 25 (1/31/2011 Response) at 2. The examiner rejected these claims as anticipated, including because a prior art reference disclosed a "SNALP wherein the cationic lipid is from about 2 mol % to about 60 mol % of the total lipid present in the particle." Ex. 26 (5/12/2011 Rejection) at 3. The examiner explained that the patentee did not provide a definition for "comprising about," and thus "'comprising about' could embrace an amount +/- 10, 20, 30 mol % of a lipid component." Ex. 26 (5/12/2011 Rejection) at 2. In response to this rejection, the patentee removed the word "about" from the claims. Ex. 27 (8/11/2011 Response) at 2.

Thus, the examiner's position was that a claimed range of "about" 50–65 mol % could potentially have variability of "+/- 10, 20, 30 mol %." When the patentee removed the word "about," it only disclaimed the very broad ranges that the examiner equated with the word "about." The patentee did not disclaim the minor variations of scientific conventions of rounding, which allow for variation of 0.5% for whole numbers such as "50".

[6] The '359 patent is a continuation of the '069 patent.

The Federal Circuit's *Actelion* decision is instructive, as the court declined to equate words of approximation (like "about") with the rules of rounding. 85 F.4th 1167. There, the defendant argued that the claim term "a pH of 13 or higher" had an absolute floor of 13. *Id.* at 1170. It argued that the absence of approximation language like "about," which was present in other claim terms, "must mean that 'a pH of 13' is *exactly* 13." *Id.* at 1171. The court rejected this argument and instructed: "[w]e reject any invitation to create a bright-line rule—either that language like 'precisely' or 'exactly' is always needed to avoid rounding or that the lack of approximation language, even when it may be found elsewhere in the claims, dictates a precise value." *Id.*

The court in *Arbutus Delaware* relied on the Federal Circuit's *Actelion* decision in finding that the removal of "about" during prosecution of the '069 patent did not disclaim rounding. 2024 WL 1434526 at *11. The *Arbutus Delaware* court explained:

> When Plaintiff removed the phrase "comprising about," it only clearly disclaimed these broader ranges and not the scientific conventions of rounding, which allow for minimal variation…The mere fact that the examiner drew a distinction between a range of "about 50–65 mol %" and "50–65 mol %" does not illuminate the narrower issue of whether a range of "50–65 mol %" could encompass values that round to those range endpoints, specifically 49.5–65.4 mol %. In short, I find no clear prosecution history disclaimer regarding the rules of rounding.

Id. As the *Arbutus Delaware* court found, the removal of "about" from the claims during prosecution of the '069 patent does not limit the plain meaning of the recited mol % ranges. Far from disavowing the "standard" rules of significant figures and rounding, as in *Viskase*, 261 F.3d at 1321-22, the amendment was made in direct response to the examiner's statement that the term "comprising about" could "embrace an amount +/- 10, 20, 30 mol % of a lipid component." Ex. 26 (5/12/2011 Rejection) at 2. Thus, the removal of "comprising about" as a modifier of "50 mol % to 65 mol %" cationic lipid did not remove rounding, but rather—per the examiner's explicit statement prompting the amendment—"+/- 10, 20, 30 mol % of a lipid component."

This case thereby contrasts starkly with those imposing additional specificity where the patentee needed to draft claims narrowly to avoid the prior art. *See, e.g., Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377, 1382 (Fed. Cir. 2000) (patentee "rel[ied] on the precise ranges of the claims to distinguish" "nearly identical" prior art (emphasis added)); *In re Fenofibrate Patent Litig.*, 910 F. Supp. 2d 708, 712 (S.D.N.Y. 2012) ("unlikely that this two-hundredths difference would have been enough for the patent examiner to award the patent"); *see also* Thompson Decl. ¶ 86-92. Nor do Plaintiffs seek to read out the claimed ranges, unlike cases like *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1374–75 (Fed. Cir. 2002) (patentee sought to negate "345F" from the claim), or to render the claimed ranges "approximations" untethered to the "numerical precision" denoted by the literal text of the claim, unlike cases like *Baxter Healthcare Corp. v. Nevakar Injectables, Inc.*, No. 21-CV-1184-CJB, 2023 WL 4175261, at *15 (D. Del. June 26, 2023).

Accordingly, the removal of "about" from the claims during prosecution does not support Defendants' construction. It had nothing to do with whether the claimed ranges are entitled to the degree of precision of their literal expression and thus cannot displace the general rules of significant digit rounding. *See, e.g., Copan Italia S.p.A. v. Puritan Medical Prods. Co.*, No. 1:18-CV-00218-JDL, 2019 WL 5699078, at *11-12 (D. Maine Nov. 4, 2019) (declining to construe "90%" as "precisely 90%" where claims were amended from "about 90%" to "90%"); *Johnson Matthey*, 2009 WL 2208214, at *4, *9 (construing "literal range" of "41-42° C" as from "40.5° C" to "42.4° C" despite absence of "about"); *accord Pacira Pharms., Inc. v. eVenus Pharms. Lab'ys, Inc.*, No. 21-CV-19829, 2023 WL 3841559, at *14 (D.N.J. June 6, 2023) ("While [5.45 to 5.55] pH levels may fall into the range of 'about 5.5,' the Court declines to arbitrarily construe 'about'

through use of rounding principles"); *see also* Thompson Decl. ¶ 92. There is no basis to adopt Defendants' construction.

D. "consisting essentially of" ('378 patent)

Plaintiffs' proposed construction	Defendants' proposed construction
Plain and ordinary meaning, *i.e.*, "consisting of only the listed ingredients and those that do not materially affect the combination and concentration of the lipid components" The basic and novel properties of the claimed invention of the '378 patent are the combination and concentration of the lipid components	Indefinite. The purported "basic and novel properties," according to the patent, include: increased activity of the encapsulated nucleic acid, improved tolerability of the formulations in vivo, significant increase in therapeutic index, and stable, compared to lipid particles having less than 50 mol % cationic lipid.
'378 Patent, Claim 1	

The use of the phrase "consisting essentially of" in a patent claim "represents a middle ground between the open-ended term 'comprising' and the closed-ended phrase 'consisting of'" and "has long been understood to permit inclusion of components not listed in the claim provided that they do not 'materially affect the basic and novel properties of the invention.'" *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003) (quoting *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998)). The parties' dispute centers on what the "basic and novel properties" of the invention claimed in the '378 patent are. Plaintiffs propose basic and novel properties of the claimed particle that are supported by the intrinsic evidence and specific to the invention of the '378 patent. Defendants argue that such properties are indefinite, but also propose several basic and novel properties that are purportedly described in the specification. Defendants' proposed properties neither accurately characterize the claimed invention of the '378 patent nor reflect the distinctions made by the patentee over the prior art.

Claim 1 of the '378 patent includes the disputed claim term and is reproduced below:

1. A nucleic acid-lipid particle ***consisting essentially of***:

> (a) an RNA;
> (b) a cationic lipid having a protonatable tertiary amine;
> (c) a mixture of a phospholipid and cholesterol of from 30 mol % to 55 mol % of the total lipid present in the particle, wherein the phospholipid consists of from 3 mol % to 15 mol % of the total lipid present in the particle; and
> (d) a polyethyleneglycol (PEG)-lipid conjugate consisting of from 0.1 mol % to 2 mol % of the total lipid present in the particle.

'378 patent claim 1 (emphasis added).

In determining the basic and novel properties of the invention, courts look to the same intrinsic evidence typically considered during claim construction. Courts may examine the specification to determine "the goal of the invention as well as what distinguishes it from the prior art." *AK Steel*, 344 F.3d at 1239-40. Courts also look to the prosecution history. *See L'Oréal S.A. v. Johnson & Johnson Consumer Cos.*, No. 12-CV-98-GMS, 2014 U.S. Dist. LEXIS 190268, at *6-7 n.2 (D. Del. Nov. 5, 2014) (finding that "the prosecution history—particularly the Patent examiner's restriction requirement, which resulted in the '354 Patent—also supports the L'Oréal's basic and novel property proposal," where "the restriction requirement confirms that stabilization of avobezone (a ketone) is a novel property").

Courts have additionally consulted the prosecution history to "determine whether an unlisted ingredient was excluded from the scope of a 'consisting essentially of' claim," which informs what the basic and novel properties are. *DePuy Mitek, Inc. v. Arthrex, Inc.*, No. 04-CV-12457-PBS, 2007 WL 9797539, at *5 (D. Mass. Jan. 31, 2007) (citing *PPG*, 156 F.3d at 1355). In *Aventis Pharma S.A. v. Hospira, Inc.*, the claims at issue recited a "composition consisting essentially of" a drug compound and other limitations, including the two solvents ethanol and polysorbate. 743 F. Supp. 2d 305, 320 (D. Del. 2010). During prosecution, the patentee explained that the claim at issue "'consists essentially of' a two-solvent system," and distinguished a prior art reference Tarr because it included a third solvent called pluronic L64. *Id.* at 358. The examiner allowed the claims, explaining that "carriers having similar characteristics as pluronic L64 [*i.e.*,

carriers that are surfactants[7]] are excluded from the claims." *Id.* The court concluded that "the use of polysorbate 80 as the sole surfactant is a basic and novel property of the invention" because the prosecution history excluded "systems where the third solvent (*i.e.*, besides polysorbate 80 and ethanol) is a surfactant." *Id.*

1. The combination and concentration of the lipid components are the basic and novel properties of the claimed invention of the '378 patent

The intrinsic evidence here makes clear that the basic and novel properties of the claimed invention of the '378 patent are the combination and concentration of the lipid components recited in the claims. Claim 1 of the '378 patent recites four lipid components—a cationic lipid having a protonatable tertiary amine, along with a phospholipid, cholesterol, and a PEG-lipid conjugate at particular concentration ranges. The prosecution history of the '378 patents confirms that the basic and novel properties of the invention are the combination and concentration of the lipid components.

During prosecution of the '378 patent, the examiner issued a single rejection, concluding that the claims would have been obvious over several prior art references. Ex. 29 (6/14/21 Rejection) at 3. The patentee did not rely on any of the formulation properties that Defendants assert to be the basic and novel properties. Rather it explained how the cited references failed to "teach or suggest the claimed combination of components present in the lipid particles at the recited concentration ranges." Ex. 30 (8/20/21 Response) at 6.

The patentee further stated that "none of the references teaches or suggests: (i) ***a four-component lipid particle*** with RNA as the payload; (ii) a cationic lipid having a protonatable tertiary amine; or (iii) RNA delivery using a lipid particle containing a cationic lipid with

[7] Pluronic L64 is a surfactant. Thompson Decl. ¶ 93.

phospholipid, cholesterol, and PEG-lipid components ***at the recited concentration ranges***." Ex. 30 (8/20/21 Response) at 10 (emphases added). In that regard, for example, the patentee distinguished the Basarkar, Tarcha, Gallie, and Arima references for failing to teach the claimed PEG-lipid conjugate. Ex. 30 (8/20/21 Response) at 7-8. The patentee further distinguished Gallie because it did not disclose the claimed PEG-lipid conjugate concentration of 0.1 mol % to 2 mol %. Ex. 30 (8/20/21 Response) at 8. Additionally, the patentee remarked that the Li reference "provides no disclosure of a four-component lipid system as claimed or the recited concentrations of lipid components." Ex. 30 (8/20/21 Response) at 9. Regarding the Semple reference, the patentee stated that it "does not teach or suggest particles with a four-component lipid system as claimed" and that it taught away from the claimed "molar ratios." Ex. 30 (8/20/21 Response) at 9. The examiner allowed the claims of the '378 patent-in-suit following the patentee's remarks. Ex. 31 (8/30/21 NOA).

The above statements show that the claimed combination and concentration of the lipid components is "what distinguishes [the invention of the '378 patent claims] from the prior art." *AK Steel*, 344 F.3d at 1239-40. The patentee repeatedly focused on the fact that the cited references failed to disclose a four-component lipid particle having the claimed lipid components, as well as a particle with lipids at the recited concentrations, where specified. The basic and novel properties of the '378 patent are therefore the claimed combination and concentration of the lipid components. *See Aventis*, 743 F. Supp. 2d at 358 (determining the basic and novel properties based on how the patentee distinguished the prior art during prosecution); *see also AK Steel*, 344 F.3d at 1239-40 (determining the basic and novel properties based on how the patentee distinguished the prior art). There are no other bases on which the patentee distinguished the claimed invention of the '378 patent from the prior art.

2. Defendants' proposed basic and novel properties should be rejected

Defendants' proposed basic and novel properties should be rejected, as they (1) improperly assume that the '378 patent is limited to a nucleic acid lipid particle having 50 mol % or more cationic lipid, and (2) involve illogical comparisons of the claimed invention of the '378 patent to itself.

According to Defendants, the basic and novel properties of the '378 patent invention "according to the patent, include: increased activity of the encapsulated nucleic acid, improved tolerability of the formulations in vivo, significant increase in therapeutic index, and stable, ***compared to lipid particles having less than 50 mol % cationic lipid***." Ex. 32 (JCCPS) at 26 (emphasis added). Thus, Defendants' proposed "basic and novel properties" require a comparison between the claimed particles of the '378 patent and "lipid particles having less than 50 mol % cationic lipid." This comparison, however, implies that the '378 patent requires 50 mol % or more cationic lipid.

Claim 1 of the '378 patent recites a "nucleic-acid lipid particle consisting essentially of" several components, including "a cationic lipid having a protonatable tertiary amine," but does not include any explicit limitation on the mol % of cationic lipid present. '378 patent claim 1. The invention of the '378 patent thus more broadly includes lipid particles having less than 50 mol % cationic lipid and the examiner examined the claims on that broader basis. Thus, the basic and novel properties cannot have involved a comparison to formulations with less than 50 mol % cationic lipid, because at least some such formulations are part of the invention as claimed in the '378 patent.

At bottom, Defendants' proposed construction is an improper attempt to shoehorn in a minimum 50 mol % cationic lipid limitation into claim 1. When the parties exchanged preliminary proposed constructions on March 21, 2024, Defendants attempted to limit the claims of the '378

patent to a minimum 50 mol % cationic lipid limitation based on two separate arguments. First, Defendants argued that the "cationic lipid having a protonatable tertiary amine" should be construed to include a numerical minimum of 50 mol % cationic lipid even though none was recited. Ex. 33 (3/21/24 Defendants' preliminary constructions) at 4. Second, Defendants argued that the "consisting essentially of" language imposed an effective 50% limitation by requiring an improvement as compared to compositions with less than 50 mol % cationic lipid. *Id.* at 4-5.

But after the court in *Arbutus Delaware* issued its claim construction order rejecting Moderna's attempt to limit the "cationic lipid" claim term to 50 mol % (Defendants' first argument here), 2024 WL 1434526, at *16, Defendants here withdrew their first argument and agreed with Plaintiffs on a construction that did not include a concentration requirement.[8] However, Defendants continue to pursue their second argument (Moderna did not even raise such an argument in the *Arbutus Delaware* case) in a continued effort to import a 50 mol % limitation into a claim that does not include such a requirement.

And if Defendants did not imply that claim 1 includes a minimum 50 mol % cationic lipid limitation, then Defendants' proposed construction would make little logical sense, as it would involve comparing the claimed invention of the '378 patent to itself. For example, a nucleic acid lipid particle that includes 47 mol % cationic lipid having a protonatable tertiary amine and also meets the other limitations of claim 1 would fall within the scope of claim 1. Such a particle cannot have "increased activity of the encapsulated nucleic acid, improved tolerability of the formulations in vivo, significant increase in therapeutic index, and stable, compared to lipid particles having less than 50 mol % cationic lipid" ***because this particle is itself*** a nucleic acid lipid particle "having

[8] The parties agreed that "cationic lipid having a protonatable tertiary amine" ('378 Patent Claim 1)" means "a lipid that carries a net positive charge at a selected pH having a protonatable tertiary amine." Ex. 32 (JCCPS) at 3.

less than 50 mol % cationic lipid." Defendants' proposal thus cannot be the basic and novel properties of the claimed invention of the '378 patent.

* * *

Plaintiffs' proposed basic and novel properties should thus be applied, as the prosecution history shows that the combination and concentration of the lipid components was the basis on which the '378 patent claims were examined, as well as the basis on which the patentee distinguished the art.

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Respectfully submitted,

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